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EXAMINER
KERR, KATHLEEN M

ART UNIT	PAPER NUMBER
1652	9

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/623,596	WACHI ET AL.	
	Examiner	Art Unit	
	Kathleen M Kerr	1652	

-- The MAILING DATE of this communication appears on the cover sh et with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *20 April 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4,5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Application Status

1. Claims 1-9 are pending in the instant application and will be examined herein. In response to the previous Office action, a sequence letter mailed on March 28, 2001, Applicants filed a sequence listing by preliminary amendment. Said amendment has been entered and brings the application into compliance with the sequence rules.

Priority

2. The instant application is granted the benefit of priority for the International Application No. PCT/JP99/01084 filed on March 5, 1999 and the foreign application Japan 10-55608 filed on March 6, 1998 as requested in the declaration. The Examiner notes that the requirements of national stage entry of the instant application had been completed (note assigned U.S. filing date) within 30 months of the earliest claimed priority date.

Without a translation of the foreign priority document, art will be considered prior art if available before March 5, 1999 for examination in the instant Office action.

Information Disclosure Statement

3. The information disclosure statements filed on December 5, 2000 (Paper No. 4) and January 2, 2001 (Paper No. 5) have been reviewed, and their references have been considered as shown by the Examiner's initials next to each citation on the attached copies.

Drawings

4. The drawings have been approved by the Draftsmen and are, therefore, entered as formal drawings acceptable for publication upon the identification of allowable subject matter.

Objections to the Specification

5. In the specification, the Abstract is objected to for not completely describing the disclosed subject matter. It is noted that in many databases and in foreign countries, the Abstract is crucial in defining the disclosed subject matter, thus, its completeness is essential. The Examiner suggests the inclusion of the full name of the protein, penicillin binding protein, and the source species, *Corynebacterium glutamicum*, for completeness.

Claim Objections

6. Claims 1-4 are objected to for an informality. In the instant methods, the use of bacteria is in culture where more than one bacterium is growing. Thus, for proper usage, the term "bacterium" should be replaced with the plural form ---bacteria--- at each occurrence.

7. Claims 6-7 and 8-9 are objected to for the following informality. The recitation of "in Sequence Listing" or "in Sequence" is extraneous because all sequences identified by SEQ ID NO must be found in the sequence listing. Deletion of these phrases is suggested.

8. Claims 8-9 are objected to for the following informality. In the last lines of both Claims 8 and 9, the phrase "an activity for binding to penicillin" is not usage. The Examiner suggests replacing this phrase with ---the ability to bind penicillin---.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1-2 and 4-7 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "wherein penicillin binding protein (PBP) does not normally function" is confusing. The specification identifies three penicillin binding proteins from coryneform and describes the third one (60 kD species) using its sequence, SEQ ID NOs:1 and 2, and a physical characteristic, MW 60 kD. It is unclear if "normally" indicates a wild-type coryneform that has no PBP genes or only has non-functional PBP proteins. Alternatively, should this method be practiced with mutant, deletion strains of coryneform? Moreover, on page 9, this phrase is defined as "a state that the L-glutamic acid production is induced in the presence of significant amounts of biotin" and "significant" is an undefined relative term. Appropriate clarification is required.

10. Claims 2-4 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In Claim 2, lines 3 and 4, reference to "**the** first temperature" and "**the** second temperature" (emphasis added) is unclear since no antecedent basis precedes these phrases in the instant claim or its parent. The Examiner suggests either preceding these phrases with a claim limitation about growth at two temperatures OR amending the claim to refer to ---a first (or second) temperature--- on lines 3 and 4.

11. Claim 3 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In line 5, the phrase "**the** PBP gene on chromosome" (emphasis added) is unclear because, particularly in the coryneform described in the specification, more than one PBP gene can be found in the chromosome and "the" refers to a particular PBP gene. Appropriate clarification is required.

12. Claim 4 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In lines 1-2, the phrase "**the** penicillin binding protein" (emphasis added) because, particularly in the coryneform described in the specification, there is more than on PBP protein and "the" refers to a particular PBP protein. Appropriate clarification is required.

13. Claim 8 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim wording in item (B) is unclear as to the limitation of "an activity for binding to penicillin". The Examiner suggests the insertion of ---wherein said protein has--- for this phrase for clarity.

14. Claim 9 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim wording in item (b) is unclear as to the limitation of "codes for a

protein having an activity for binding to penicillin". The Examiner suggests the insertion of ---wherein said DNA--- for this phrase for clarity.

15. Claim 9 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "stringent condition" is defined in the specification on pages 25-26; however, this definition is unclear as to the metes and bounds of "specific hybridization". This definition is particularly important because all DNA will hybridize to all other DNA at some condition based on the natural affinity charged molecules have for each other.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

16. Claims 1-7 are rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant claims are drawn to methods of producing glutamate using a coryneform modified to delete penicillin binding protein (PBP) function or coryneform that do not natively contain any PBPs.

To satisfy the written description aspect of 35 U.S.C. § 112, first paragraph, for a claimed genus of molecules, it must be clear that: (1) the identifying characteristics of the claimed

molecules have been disclosed, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these; and (2) a representative number of species within the genus must be disclosed. The instant specification discloses a PBP3 deletion coryneform strain, but this strain would not totally lack PBP function since the instant specification teaches that coryneform contains more than one PBP having two other molecular weight proteins that bind penicillin. Thus, no species are disclosed for use in the instant methods.

17. Claim 4 is rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant claim is drawn to methods using a PBP protein with a temperature sensitive mutation. Although the genus of PBPs with temperature sensitive mutations is discussed in the specification, there is no evidence that any representative species of such a large and varied genus was in the possession of the inventors at the time of filing.

To satisfy the written description aspect of 35 U.S.C. § 112, first paragraph, for a claimed genus of molecules, it must be clear that: (1) the identifying characteristics of the claimed molecules have been disclosed, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these; and (2) a representative number of species within the genus must be disclosed. The specification does not disclose any representative species of PBPs

with temperature sensitive mutations. Moreover, the structural characteristics of such a species are unknown. Thus, Claim 4 lacks adequate written description.

18. Claims 8 and 9 are rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 8 and 9 drawn to DNA sequence encoding penicillin binding proteins (PBPs) without any particular structural limitations. In Claim 8, the claim limitation concerning *any* number of mutations removes any real limitation of similarity to a sequence encoding SEQ ID NO:2. In Claim 9, the hybridization claim language in unclear (see above).

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these.

The instant specification discloses DNA sequences encoding PBPs, that is SEQ ID NO:1 and any DNA encoding SEQ ID NO:2. Applicants have fully described the genus relating to said SEQ ID NOs with both sequence identity limitations and functional limitations (i.e., having the ability to bind penicillin). However, the genus of the instant claims also contains DNA sequences within the functional limitations, but having any structure (sequence). Applicants have not fully described a genus that has functional limitations in the absence of sequence identity limitations.

19. Claims 1-2 and 4-7 are rejected under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for methods using coryneform whose PBP3 gene (60 kD species) is deleted (see specification Example 4) and a plasmid containing a PBP gene, does not reasonably provide enablement for methods using coryneform whose entire PBP function is deleted. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the coryneform for use in the methods of the invention commensurate in scope with these claims. The instant claims are drawn to methods of producing glutamate using a coryneform modified to delete penicillin binding protein (PBP) function or coryneform that do not natively contain any PBPs. To practice such methods to the full extent of their scope, one of skill in the art would be required to perform undue experimentation.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as

routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

No guidance or working examples are offered to identify and delete other PBP genes from coryneform. No guidance or working examples are offered to identify a "PBP-free" coryneform strain. The state of the prior art is very limited with respect to PBPs in coryneform and their effects. While the skill in the art is high considering the ability to screen by virtue of the covalent binding of penicillin and penicillin binding proteins, the number of PBPs in coryneform is wholly unpredictable as is the likelihood of finding a native deletion strain. Thus, the instant claims are not enabled to the full extent of their scope.

The Examiner notes that Claim 3 is omitted from the instant rejection. Due to the lack of clarity of Claim 1, the Examiner has not required that PBP function be wholly deleted in the cells of the methods of Claim 3. A claim drawn to a method of making glutamate using coryneform

whose PBP3 gene, SEQ ID NO:1, is deleted or otherwise non-functional, optionally containing an additional PBP gene on a temperature-controlled plasmid would be enabled and described in the instant specification.

20. Claim 4 is rejected under 35 U.S.C. § 112, first paragraph, enablement, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The instant claim is drawn to methods using a PBP protein with a temperature sensitive mutation. No such protein is described in the specification. One of skill in the art would be required to perform undue experimentation to obtain such a mutant for practicing the claimed methods.

The factors to be considered in determining whether undue experimentation is required are summarized above.

No examples or guidance is presented in the specification for the production of a temperature sensitive mutant of PBP3 or any other coryneform PBP gene. The state of the art of producing temperature sensitive mutants is wholly random wherein no molecular structure of the protein is known. Since the instant specification appears to be the first disclosure of PBPs in coryneform and the specification contains no structural information other than linear sequence, the ability to produce a temperature sensitive mutant is wholly unpredictable. Thus, Claim 4 is not enabled.

Claim Rejections - 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

21. Claims 8-9 are rejected under 35 U.S.C. § 102(b) as being anticipated by Cole *et al.* (GenBank Accession Number Z95388 "Mycobacterium tuberculosis H37Rv complete genome, segment 96/162" created May 14, 1997) as evidenced by Cole *et al.* (GenBank Accession Number B70886 "probably penicillin binding protein – Mycobacterium tuberculosis (strain H37RV)" created July 17, 1998). The instant claims are drawn to a DNA sequence encoding penicillin binding proteins (PBPs) without any particular structural limitations; the Examiner sets forth the rejection as if some sequence similarity to SEQ ID NOs:1/2 is required.

Cole *et al.* teach a DNA encoding a PBP from base pair 34023 to 32742. This sequence is 22% identical to SEQ ID NO:1 having 58% local similarity; this sequence is 45% identical to a DNA that encodes SEQ ID NO:2 having 72% similarity.

Conclusion

22. Claims 1-9 are rejected for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kathleen M Kerr whose telephone number is (703) 305-1229. The examiner can normally be reached on Monday through Friday, from 8:30am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathupura Achutamurthy can be reached on (703) 308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-0294 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

PONNATHAPU ACHUTAMURTHY
SUPERVISORY PATENT EXAMINER
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KMK
December 15, 2001